## Mortality and Air Pollution: Associations Persist with Continued Advances in Research Methodology

*(See Neas et al., p. 629; Lee and Schwartz, p. 633; and Fairley, p. 637)*

In this issue of *Environmental Health Perspectives* there are papers by Fairley, Neas et al., and Lee and Schwartz. Although these papers present different approaches, they provide a reasonable representation of state-of-the-art epidemiologic research that evaluates daily changes in mortality and air pollution. The authors of these papers include investigators who have been primary contributors to the development of this research.

The earliest and most methodologically simple studies that evaluated day-to-day changes in mortality associated with air pollution were studies that focused on severe air pollution episodes. These studies simply compared death counts for several days or weeks before, during, and after pollution episodes. Substantially elevated cardiopulmonary mortality associated with severe air pollution episodes in Meuse Valley, Belgium, in 1930 (*1*); Donora, Pennsylvania, in 1948 (*2*); and London, England, in 1952 (*3*) clearly demonstrated a link between mortality and extremely elevated concentrations of particulate and/or sulfur oxide air pollution.

In the 1970s and 1980s, a few studies were reported that involved collecting daily mortality and pollution data from a single city or community for several years and analyzing correlations in the data (*4*). Such an approach did not require extreme pollution episodes and did allow for evaluation of potential mortality effects of relatively low, more common levels of pollution. Correlations between daily mortality and air pollution were observed, but these studies suffered from very limited pollution data and somewhat inadequate statistical methods. In the early 1990s, Fairley (*5*), Schwartz and Dockery (*6–8*), and a few other researchers (*9,10*) reported the results of several daily time–series mortality studies using more advanced, uniform, and rigorous statistical modeling techniques. The primary statistical approach was formal time–series modeling of count data using Poisson regression. These studies indicated a link between daily mortality counts and particulate air pollution, even at pollution levels well below prevailing ambient air quality standards.

There were several questions and concerns that reflected legitimate skepticism about the inherent limitations of these studies: *a*) Could the results be replicated? *b*) Were the observed air pollution/mortality associations due to biased analytic approaches or statistical modeling techniques? *c*) Were these associations due to confounding because of inadequate control of long-term time trends, seasonality, weather, or some other pollutant? *d*) Were these associations biologically significant or plausible? *e*) Could nonspurious air pollution–mortality associations really be observed at pollution levels well below U.S. ambient air quality standards? *f*) Is there a threshold level of air pollution below which there are no health effects?

Subsequent research efforts, including the three mortality and air pollution papers in this issue, have at least partially addressed some of the above questions and concerns. The results have been largely replicated by other researchers (*11*), and more importantly, similar associations have been observed in many other cities with very different climates, weather conditions, and pollution mixes, as discussed in numerous recent reviews (*4,12–17*). Furthermore, increasingly rigorous and sophisticated statistical time–series modeling techniques have also been used to try to better control for potential confounders. For example, generalized additive models (GAM) that use nonparametric smoothing have allowed for highly flexible fitting of seasonality and long-term time trends as well as nonlinear associations with weather variables such as temperature and humidity (*18–20*). These nonparametric smoothing approaches have allowed for modeling flexible nonlinear exposure–response relationships with air pollution to explore for a no-effects threshold. A well-defined threshold has not been consistently observed. The exposure–response relationship between particulate air pollution and mortality has generally been near linear. Synoptic weather modeling has also been used in some of the studies (*20,21*). The air pollution effects generally persisted after controlling for weather by either nonparametric smooths of temperature and humidity or controlling for synoptic weather patterns.

Fairley's original analysis (*5*) of the Santa Clara, California, data reported in 1990 was one of the early works using daily time–series Poisson regression to analyze daily mortality counts and air pollution. His analysis of more recent data from the same metropolitan area, reported in this issue, takes advantage of many of the more recent advances in time–series modeling techniques. The results are similar to his original findings.

The two case-crossover studies by Neas et al. and Lee and Schwartz, reported in this issue, provide an interesting alternative approach to analyzing mortality effects of short-term exposure to air pollution. Rather than using time–series analysis to evaluate associations between daily death counts and air pollution, these two studies use a clever adaptation of the common case–control design. Both papers describe this approach in some detail. Basically, this approach matches exposures at the period of time of death (case period) with one or more periods when the death did not occur (control periods) and evaluates potential excess risk using conditional logistic regression. Deceased individuals essentially serve as their own controls. By choosing control periods on the same day of the week and within 1–3 weeks of death, this approach restructures the analysis such that day of week, seasonality, long-term time trends, and changes in population size and composition are dealt with by design rather than by statistical modeling. Because this approach focuses on individual deaths rather than death counts, there are more opportunities to evaluate factors that may modify or influence the mortality effects of air pollution.

The case-crossover approach has some drawbacks. The results can be sensitive to the selection of control periods, especially when clear time trends exist. Neas et al. and Lee and Schwartz suggest choosing symmetric control periods both before and after the date of death. Using a control period following the time of death, however, is somewhat conceptually unappealing. Also, the case-crossover approach has lower statistical power due largely to the loss of information from control periods that cannot be included in the analysis.

Although the three mortality and air pollution studies in this issue of *EHP* contribute to the many previous studies that have evaluated day-to-day changes in mortality associated with air pollution, they do not provide substantial information on the specific pollutant or mix of pollutants responsible for the observed mortality effects or biological plausibility. For example, in the Santa Clara analysis, Fairley evaluated a wide range of air pollutants and found the strongest mortality associations with particles, especially fine particles (≤ 2.5 μm in aerodynamic diameter; $PM_{2.5}$) including ammonium nitrate particles. In Philadelphia, Pennsylvania, only total suspended particulates (TSP) were analyzed by Neas et al. Lee and Schwartz analyzed TSP, $SO_2$, and $O_3$ in Seoul, Korea, and mortality was most consistently associated with $SO_2$. The authors suggested that $SO_2$ may be acting as the better indicator of fine particles in Seoul. Recent reviews (*4,12–17*) of the overall epidemiologic evidence support a probable link between fine combustion-related particulate air pollution and cardiopulmonary disease and mortality. Also, several recent studies have reported that chronic long-term exposure to inhalable or fine particulate pollution is associated with an elevated risk of mortality (*22–25*). Nevertheless, there is remaining uncertainty about the role of chemistry versus size of the particles and the role of co-pollutants including $O_3$, CO, $SO_2$, $NO_2$, and others.

There is also substantial uncertainty with regard to the biologic plausibility of these associations. Biologic plausibility is enhanced by the observation of a coherent cascade of cardiopulmonary health effects and by the fact that noncardiopulmonary health end points are not typically associated with the air pollution. An overall review of the literature (*4,12–17*) reveals that a remarkable cascade of cardiopulmonary health end points has been observed to be associated with day-to-day changes in particulate air pollution. In addition to cardiopulmonary mortality, particulate air pollution has been associated with emergency room and physician's office visits for asthma and other respiratory disorders, hospital admissions for cardiopulmonary disease, increased reported respiratory symptoms, and decreased lung function. Recently, there have been studies that have attempted to look at specific physiologic end points, in addition to lung function, such as plasma viscosity (*26*), hypoxemia and heart rate (*27*), heart rate variability (*28,29*), and acute inflammatory responses (*30–31*). However, more research on the pathophysiologic pathway linking cardiopulmonary mortality and particulate air pollution clearly should be conducted.

It is not clear that the case-crossover design is necessarily superior or inferior to the various advanced time–series approaches, but it is an interesting and clever alternative approach. What does appear clear is that the various reasonable approaches and methods provide similar results, contributing further evidence that the associations between daily mortality and ambient air pollution are relatively robust and are probably not due to methodologic bias or confounding by day of week, seasonality, long-term time trends, or weather variables. A better understanding of the specific pollutants or mix of pollutants responsible for the adverse health effects and a better understanding of the biological mechanisms involved are needed.

**C. Arden Pope III**
Brigham Young University
Provo, Utah
E-mail: cap3@email.byu.edu

### References and Notes

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## Relationship between Ozone and Respiratory Health in College Students: A 10-Year Study

*(See Galizia and Kinney, p. 675)*

Ozone is the most persistent, intractable air pollutant in urban air. In 1995, over 70 million people in the United States lived in areas not meeting the 1-hr U.S. Environmental Protection Agency (EPA) ozone standard (*1*). In 1997 the EPA tightened the standards for ozone to 0.08 ppm averaged over 8 hr.

It is well known that short-term (2–7 hr) exposures to ozone at 0.08–0.2 ppm in